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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/683,258	12/05/2001	Kemin Zhou	3418	1011

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EXAMINER	
ZHOU, SHUBO	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 05/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/683,258	ZHOU, KEMIN	
	Examiner	Art Unit	
	Shubo (Joe) Zhou	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2004 and 01 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21 and 23-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21 and 23-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 May 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 12/16/04 and 3/1/05 has been entered.

Claims 21 and 23-32 are currently pending and under consideration

New Matter

2. The amendment filed May 9, 2002 to Figure 3 of the drawings is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. Statute 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material, which is not supported by the original disclosure, is as follows:

The amended Figure 3 introduces two nucleic acid sequences referred to as SEQ ID NO:05 and SEQ ID NO:06 therein, which are not present in the originally filed Figure 3, nor in the specification originally filed on December 5, 2001.

Applicant is required to cancel the new matter in the reply to this Office Action.

Sequence Rules Compliance

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). Such sequence is present in Figure 1b. However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reasons:

As set forth above, the sequences of SEQ ID NOs: 5 and 6 are introduced into the disclosure of the application as new matter, and are required to be canceled. Applicants are advised that if such sequences are canceled as new matter from the disclosure, a paper copy and a computer readable form of a new Sequence Listing that reflects the cancellation of SEQ ID NOs: 5 and 6, as well as a new statement under 37 CFR 1.821(f), are required to comply with the sequence rules set forth in 37 CFR 1.821(a)(1) and (a)(2). Failure to comply with these requirements may result in ABANDONMENT of the application under 37 CFR 1.821(g).

Specification

4. The specification is objected to because of the following:

The phrases *5"-phosphorylated* and *the hydroxyl radical"s* on page 14 are confusing. It seems that " ' " should be used in place of " " ".

It is noted that the application serial numbers of more than 70 US patent applications are recited on page 20 and other places of the specification. Applicants are request to update the status of these US applications by amendment to the specification.

Appropriate correction is required.

Drawings

5. As noted above, the sequences of SEQ ID NO:5 and SEQ ID NO:6 introduced to Figure 3 in the amendment filed 5/9/02 are new matter and are to be canceled. An amended Figure 3 reflecting the cancellation of the sequences is required.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 21 and 23-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pugh et al. (Genome Biology, Vol. 2, pages 1013.1-1013.3, 2001) in view of Walt, D.R. (Science, Vol. 287, pages 451-452, 1/21/2000).

The claims are drawn to a method for obtaining a profile of protein binding to genomic DNA of a biological sample, comprising obtaining a plurality of candidate genomic fragments by

DNA foot printing from genomic DNA bound by a plurality of proteins, eliminating unbound genomic DNA, and detecting the candidate fragments by hybridizing with a collection of nucleic acid probes that are immobilized on a collection of beads or optical fibers.

As set forth in the previous Office action mailed 5/11/04, page 3, Pugh et al. disclose binding transcription factors, which are proteins, to their DNA on a genomic-wide scale in yeast as a biological sample (p. 1013.1 , col. 1, second paragraph), which represents a profile of such binding. Pugh et al. disclose using chromatin immuno-precipitation (ChlP) assay and DNA microarrays for detection of the DNA bound to the proteins (p. 1013.1, col. 1, second paragraph). The instant specification defines a "candidate fragment" as "a nucleic acid fragment that contains information about protein nucleic acid interactions" (paragraph 0022). Pugh et al. disclose covalently cross-linking proteins to DNA (a well known form of in vivo footprinting), purifying the cross-linked DNA via antibodies (elimination of unbound genomic DNA), fluorescently labeling the enriched DNA fragments (candidate fragments), and detecting them via hybridization to DNA probes on a glass slide of microarray (p. 1013.1, col. 1, third paragraph to col. 2, first paragraph). Pugh et al. further disclose various transcription factors binding to genomic regions (page 1013.2, col. 2, second paragraph) which represents DNA bound by a plurality of proteins. Pugh et al. also disclose that 10 regions were bound by Gal4; 29 regions were bound by Ste12; 163 regions were bound by Swi4 and 87 regions were bound by MBF transcription factor (page 1013.2, col. 2, second paragraph) wherein the later two data figures represent at least 50 proteins binding to genomic regions. Pugh et al. disclose the use of intergenic and intragenic (open reading frame) probes (p. 1013.1, col. 2, first paragraph), which means the genomic sequences of interest contain genic regions. Pugh et al. disclose that genome-

wide location analysis coupled with gene-expression profiling and searches for consensus sites will potentially identify direct effectors of complex gene expression program (.p. 1013.3, col. 1, third paragraph).

Pugh et al., however, do not explicitly disclose detecting of the candidate fragments by hybridizing to nucleic acid probes that are immobilized on a collection of beads or optical fibers.

Walt teaches a new nucleic acid array referred to as bead-based fiber-optic array for nucleic acid hybridization and detection. Walt discloses that bead arrays are assembled on an optical fiber substrate. See title and page 451, left column. Walt also teaches that fiber-optic oligonucleotide arrays can be prepared by attaching DNA probes to microspheres and then filling each well with a microsphere carrying a different DNA probe. See the paragraph bridging page 451 and 452. Walt also disclose that typical image arrays contain between 5000 and 50,000 individual fibers. See page 451, right column.

Walt states that the advantage of optical fiber sensors are their small size and flexibility, and such features enable the sensors to be placed directly into sample solutions of DNA for immobilizing DNA thereon, rather than bringing the DNA samples to the substrate surface as in the case of glass slide microarray. See page 451, middle column. Thus, sample sizes of about 1 microliter enable DNA to be detected after a limited number of amplification cycles. See page 452, middle column, bottom paragraph. In addition, Walt discloses that another advantage of bead-based optical fiber array is that a simple high temperature denaturation or organic solvent treatment can accomplish dehybridization, and hence fiber-optic microarrays have been used for over 100 hybridization-dehybridization cycles with less than 2% degradation. See page 452, right column.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method by Pugh et al. such that bead-based optical fiber arrays are used in place of glass slide array to take full advantage of the superiorities of optical fiber arrays as disclosed by Walt and detailed above.

As to claims 23-28, which recite a particular number of nucleic acid probes, such as 10,000 in claim 23, or recite a different length for the nucleic acid probe on the array, the difference between what is disclosed by Pugh et al. and Walt and the what is required by the instant claims is the size of the microarray with different numbers and length of the probes thereon. The court in *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976) held that "mere scaling up of a prior art process capable of being scaled up, if such were the case, would not establish patentability in a claim to an old process so scaled." 531 F.2d at 1053, 189 USPQ at 148. Further, in *Gardner v. TEC Systems, Inc.*, 725 F.2d 1338, 220 USPQ 777 (Fed. Cir. 1984), cert. denied, 469 U.S. 830, 225 USPQ 232 (1984), the Federal Circuit held that, where the only difference between the prior art and the claims was a recitation of relative dimensions of the claimed device and a device having the claimed relative dimensions would not perform differently than the prior art device, the claimed device was not patentably distinct from the prior art device. Also see MPEP 2144.04. In the instant case, claims 23-28 merely recite step using a microarray that has a different size, and thus with different number of probes, or a different length for the probes immobilized thereon than what is disclosed in the cited references, and is thus not patentably distinct from the methods disclosed by a combination of Pugh et al. and Walt.

8. Claims 29-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pugh et al. (Genome Biology, Vol. 2, pages 1013.1-1013.3, 2001) in view of Walt, D.R. (Science, Vol. 287, pages 451-452, 1/21/2000), as applied to claims 21 and 23-28 above, further in view of Shoemaker et al. (Nature, Vol. 409, pages 922-923, 2001).

The claims are drawn to a method for obtaining a profile of protein binding to genomic DNA of a biological sample, comprising obtaining a plurality of candidate genomic fragments by DNA foot printing from genomic DNA bound by a plurality of proteins, eliminating unbound genomic DNA, and detecting the candidate fragments by hybridizing with a collection of nucleic acid probes that are immobilized on a collection of beads or optical fibers. The probes on the arrays are oligonucleotides that tile genomic sequences of interests.

As applied to claims 21 and 23-28 above, the combination of Pugh et al. and Walt teaches such a method. However, Pugh et al. and Walt et al. do not explicitly recite using a microarray have probes thereon that tile a genomic region of interest.

Shoemaker et al. disclose a method of using tiling arrays containing overlapping oligonucleotides that blanket an entire genomic region of interest for assaying gene expression data. Shoemaker et al. state that Such approach of using tiling arrays provides a higher resolution view of gene structure and potentially reveals exons not identified by current gene prediction algorithms and also provide information about alternative splicing.

Since the combination of Pugh et al. and Walt provide a method of finding the genomic locations of the binding site of transcription factors (proteins), and since Pugh et al. disclose that transcription factors would bind to both intergenic and intragenic sites but the intragenic sites are not bound by their cognate factor and are not functional, it would have been obvious to one of

ordinary skill in the art that a higher resolution of the gene structure in terms of the exact location of the protein binding would have been desired. Thus, one having ordinary skill in the art would have been motivated by Shoemaker et al. to modify the methods of Pugh et al. and Walt to utilize tiling arrays to blanket the regions of interest for the detection of the genomic regions that bind to the transcription factors to take full advantage of the tiling arrays in order to determine the precise location of the protein binding site in the genome, intergenic or intragenic, and if it is intergenic, whether it is in the promoter of the gene.

As to claim 32, which recite at least one of the binding proteins is unknown, Pugh et al. disclose that "although SBF appears to be bound to many intergenic sites, it is perplexing that deletion of its Swi4 subunit has little effect on the expression of putative SBF target genes," and Pugh et al. suggest that it is possible that additional or redundant transcription programs direct the expression of these genes." See page 1013.3, left column. Thus, Pugh et al. implicitly disclose or suggesting other unknown proteins involving in the transcription of, and thus binding to, these genes, in addition to SBF.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shubo (Joe) Zhou, whose telephone number is 571-272-0724. The examiner can normally be reached Monday-Friday from 8 A.M. to 4 P.M. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D., can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Any inquiry of a general nature or

relating to the status of this application or proceeding should be directed to Patent Analyst Tina Plunkett whose phone number is (571) 272-0549.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shubo (Joe) Zhou, Ph.D.

Patent Examiner

ARDIN H. MARSCHEL
PRIMARY EXAMINER
5/5/05